CHEMICAL LIBRARIES IN *DRUG DISCOVERY* PROJECTS

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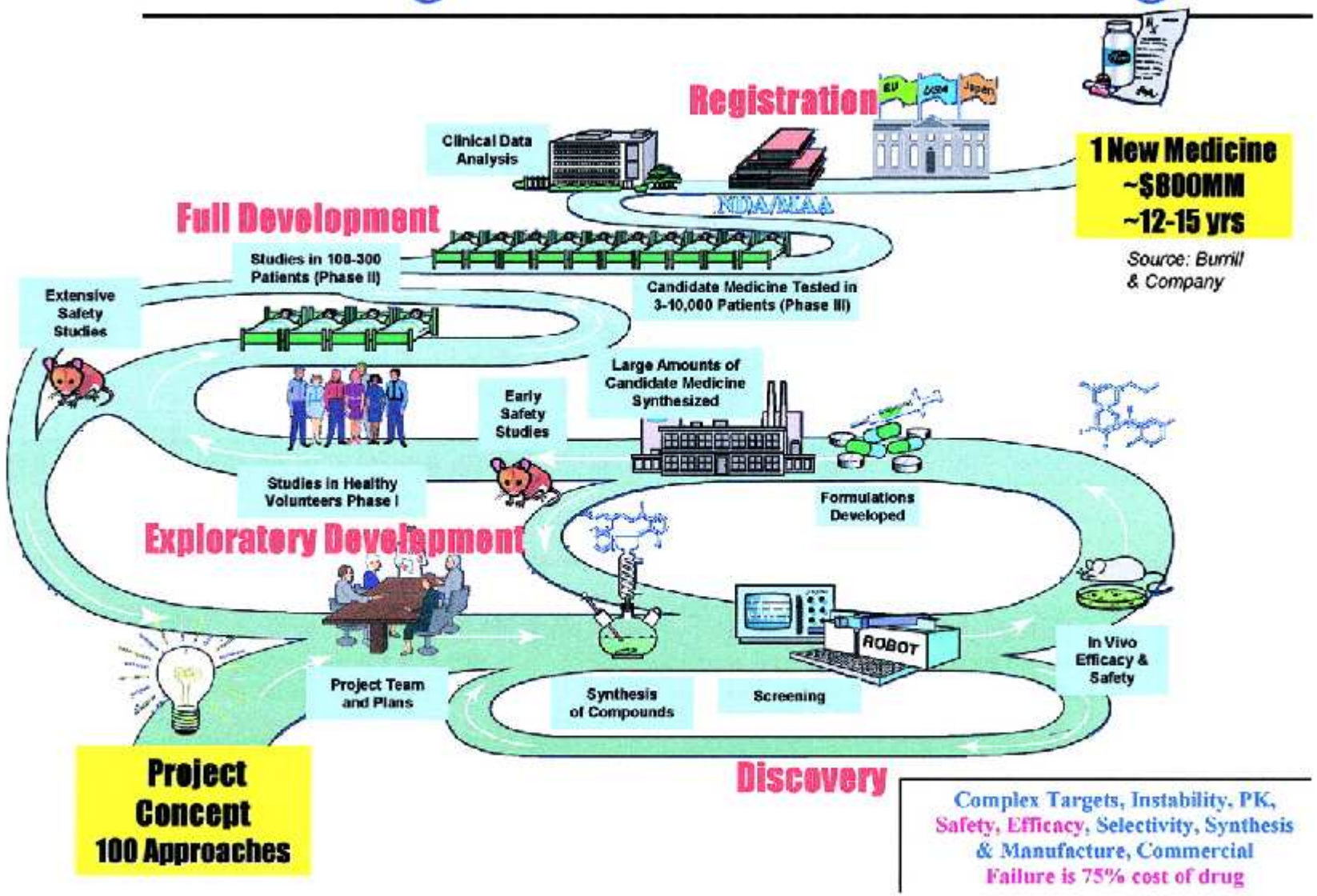
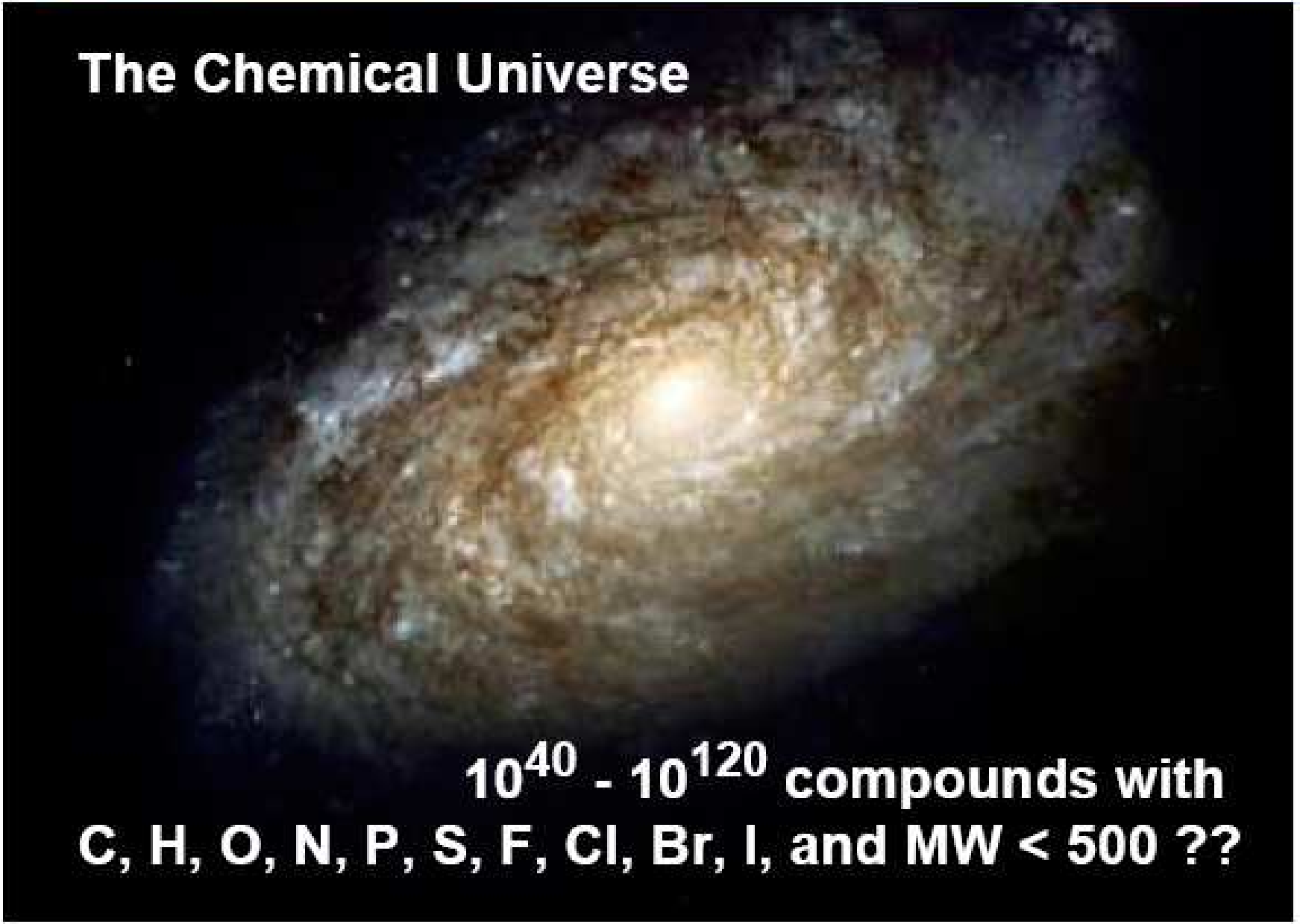
The Long Path from Idea to Drug



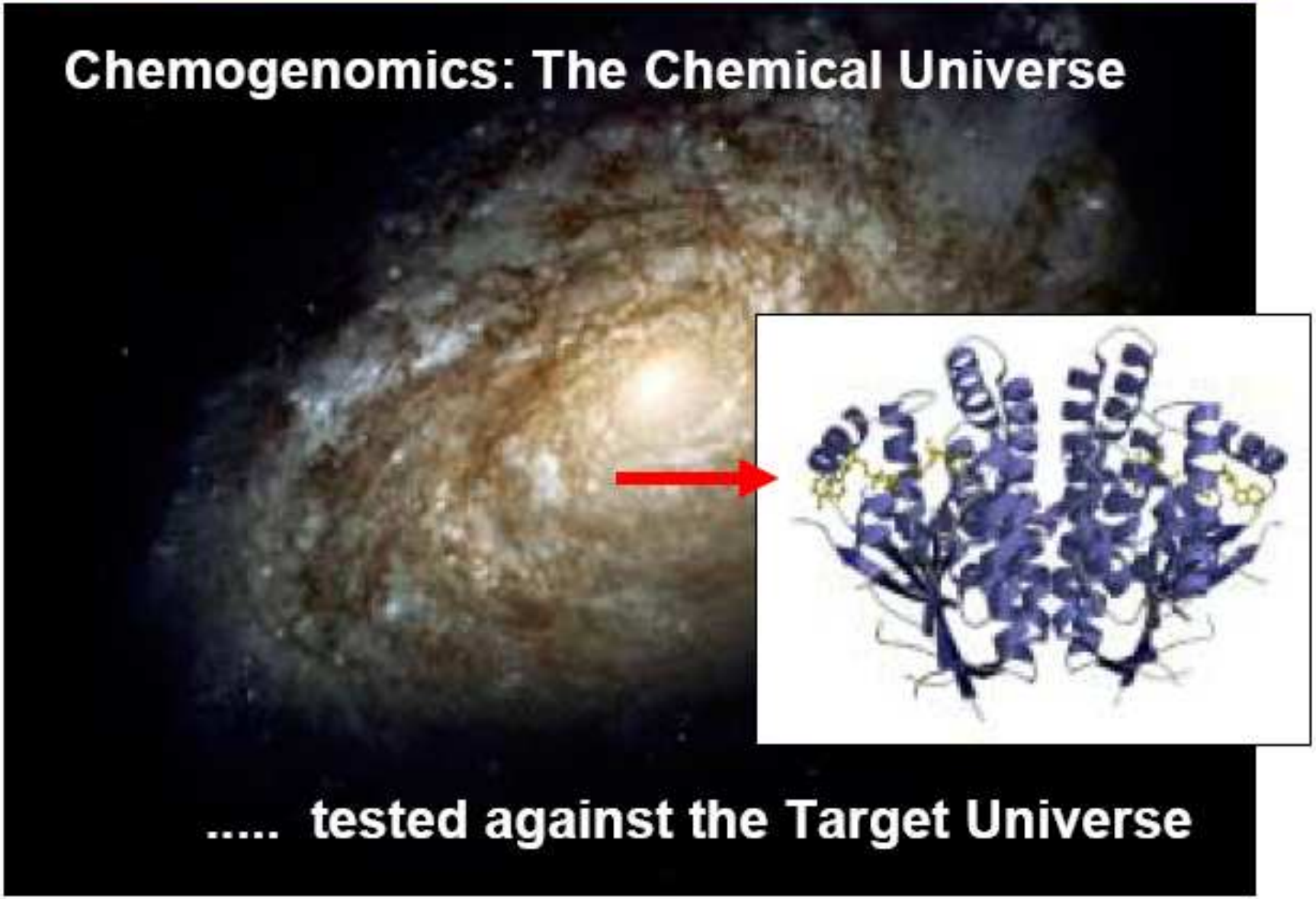
From: Scott P. Kennedy and B. J. Bormann, *Experimental Biology and Medicine* 231:1690-1694 (2006)

OUTLINE

- CHEMICAL DIVERSITY AND BIOLOGICAL DIVERSITY
- CHEMICAL LIBRARIES: AVAILABILITY / COMPOUND SELECTION
- A CASE STUDY

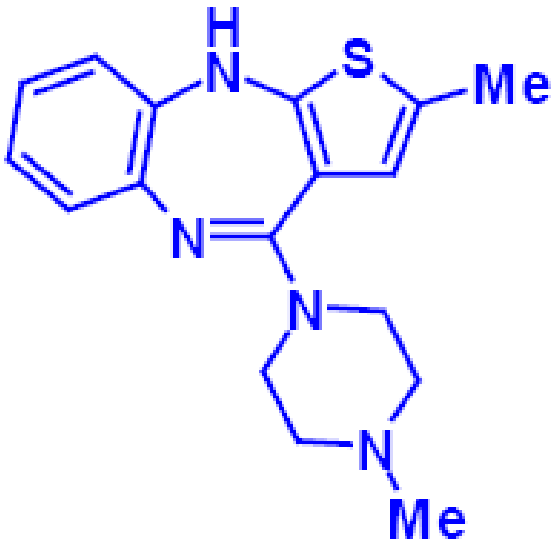

The Chemical Universe
10^{40} - 10^{120} compounds with
C, H, O, N, P, S, F, Cl, Br, I, and MW < 500 ??

Chemogenomics: The Chemical Universe



..... tested against the Target Universe

Many Ligands Bind to Several GPCRs

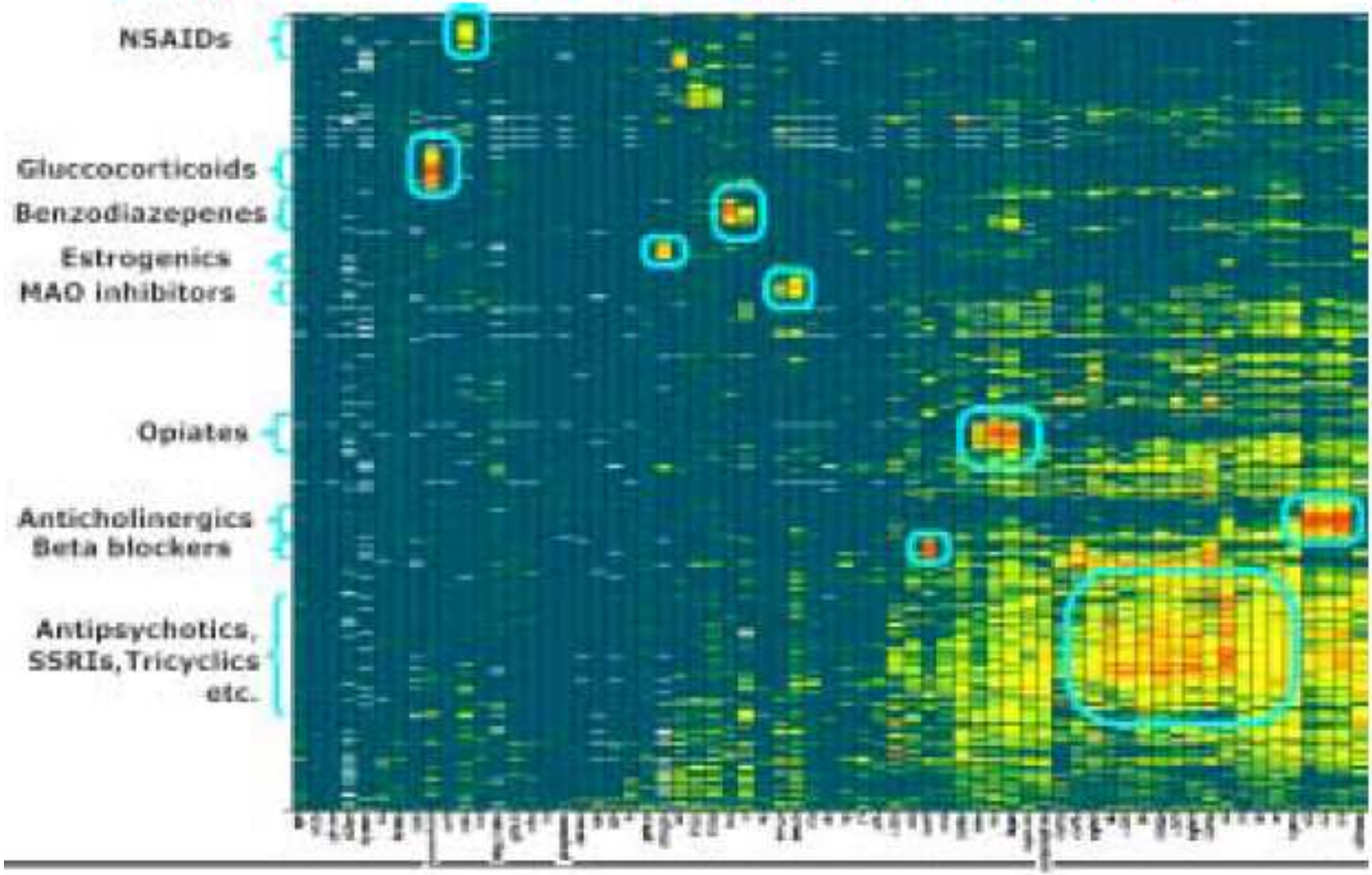


Olanzapine, a clozapine-like „atypical“ neuroleptic with a promiscuous binding pattern

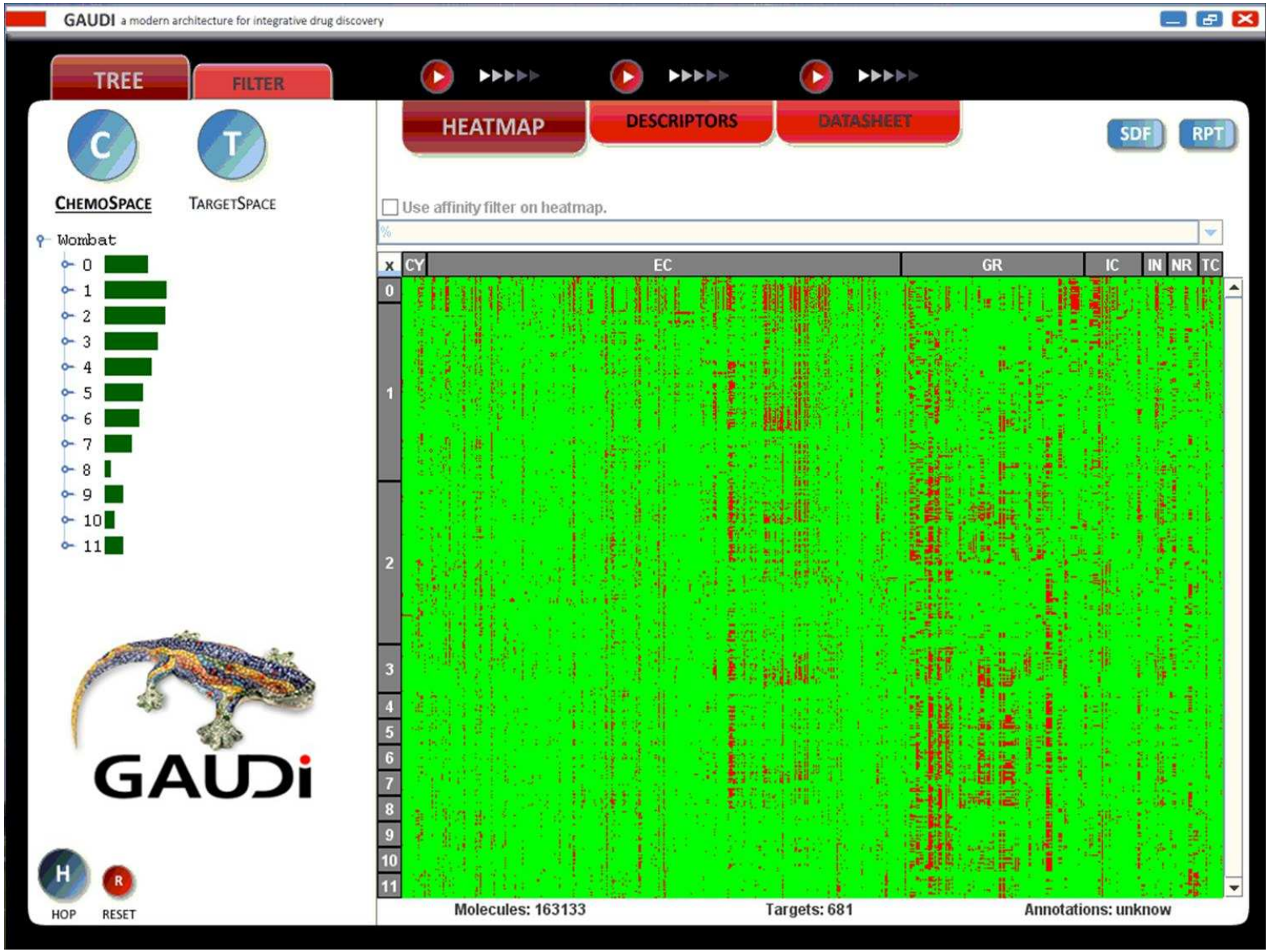
a) F. P. Bymaster et al., Neuropsychopharmacology 14, 87-96 (1996)
b) F. P. Bymaster et al., Schizophrenia Research 37, 107-122 (1999)

	a)	b)
K_i 5-HT$_{2A}$ =	4 nM	2.5 nM
K_i 5-HT$_{2B}$ =		12 nM
K_i 5-HT$_{2C}$ =	11 nM	2.5 nM
K_i 5-HT$_3$ =	57 nM	
K_i dop D$_1$ =	31 nM	119 nM
K_i dop D$_2$ =	11 nM	
K_i dop D$_4$ =	27 nM	
K_i musc M$_1$ =	1.9 nM	2.5 nM
K_i musc M$_2$ =	18 nM	18 nM
K_i musc M$_3$ =	25 nM	13 nM
K_i musc M$_4$ =	13 nM	10 nM
K_i musc M$_5$ =		6 nM
K_i adr α_1 =	19 nM	19 nM
K_i adr α_2 =	230 nM	
K_i hist H$_1$ =	7 nM	7 nM

Bioprint Database (Cerep; www.cerep.fr)



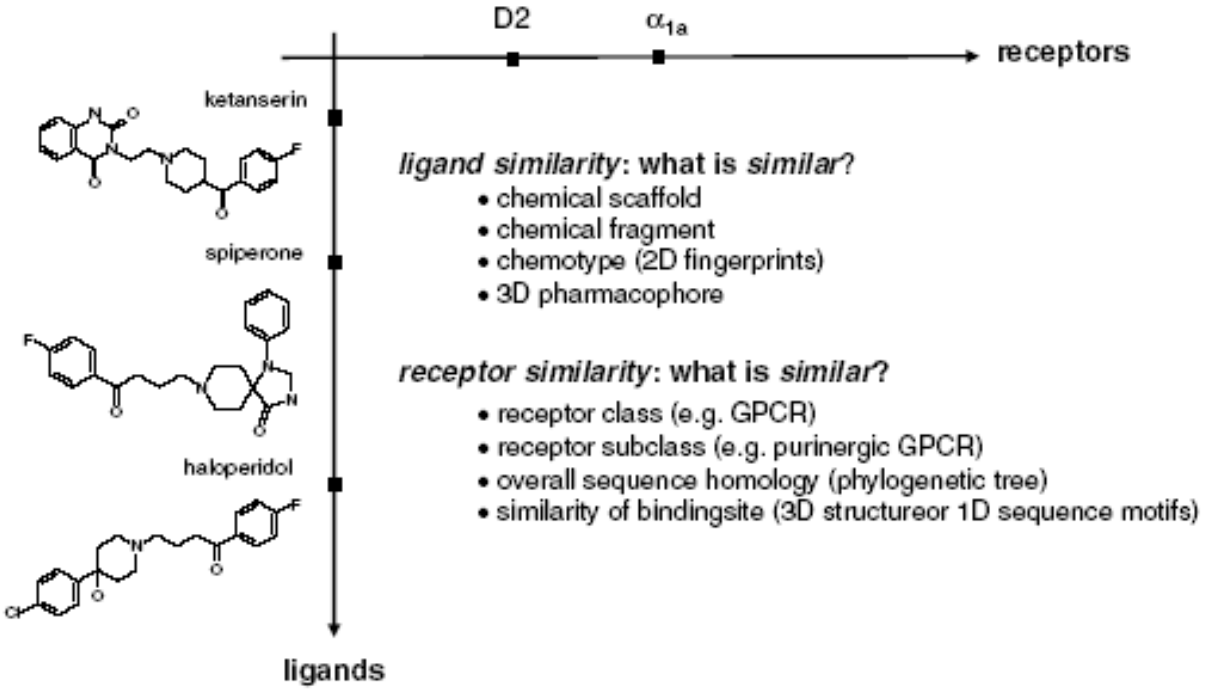
Jordi Mestres, IMIM / Chemotargets (http://www.chemotargets.com/)



Chemogenomic approaches to drug discovery: similar receptors bind similar ligands

T Klabunde

British Journal of Pharmacology (2007) 152, 5–7



- CHEMICAL DIVERSITY AND BIOLOGICAL DIVERSITY
- **CHEMICAL LIBRARIES: AVAILABILITY / COMPOUND SELECTION**
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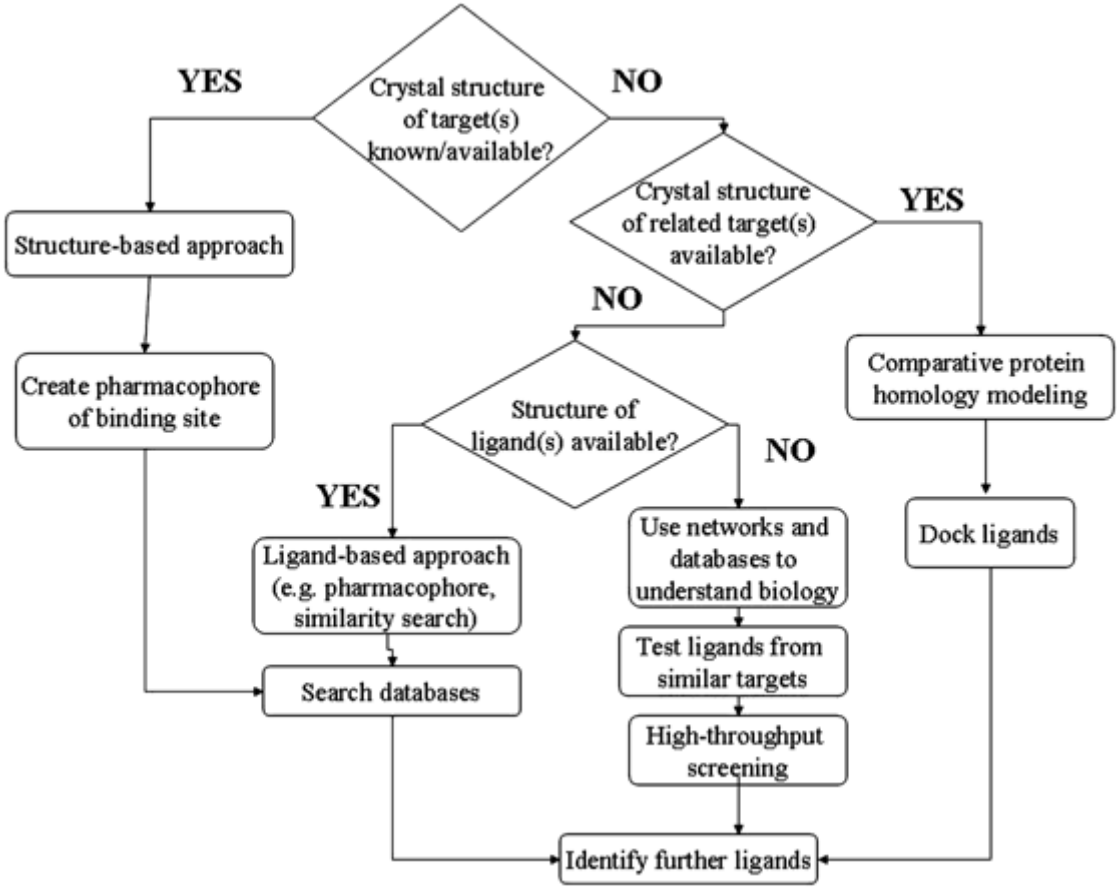
Target Structure-based ligand design / Ligand-based design



Leadlikeness and structural diversity of synthetic screening libraries

Herman J. Verheij

Molecular Diversity (2006) 10: 377–388

Table 1. List of supplier libraries that were analyzed in this study

Supplier	Issue date	Web address	Library size[e]
AKOS	Dec-04	www.akosgmbh.de	251819
Art-Chem	Q1/2005[a]	www.art-chem.com	113793
ASDI	Jan-05	www.asdi.net	110121
Asinex gold	Jan-05	www.asinex.com	224552
Asinex platinum	Jan-05	www.asinex.com	111598
A-Synthese biotech	May-04	www.a-syntese-biotech.dk	16122
Aurora	Jan-05	www.aurora-feinchemie.com	29502
BioFocus	Mar-05	www.biofocus.com	20280
Bionet	01/2005[b]	www.keyorganics.ltd.uk	43179
Biotech corp of America	Mar-05	www.biotech-us.com	60047
Cerep	Apr-05	www.cerep.com	21105
Chem T&I	Feb-05	www.chemti.com	484097
Chembridge	Dec-04	www.chembridge.com	426576
Chemdiv	Nov-03	www.chemdiv.com	136691
Chemical block	Jan-05	www.chemical-block.com	101266
Chemstar	Jan-04	www.chemstar.ru	60213
Comgenex	Mar-05	www.comgenex.com	161157
EMC microcollections	Mar-05	www.microcollections.de	23411
Enamine	11/2003[c]	www.enamine.net	114835
Exclusive chemistry	Jan-05	www.exchemistry.com	860
FCHC	Feb-05	www.ark.chem.ufl.edu	30564
Innovapharm	May-05	innovapharm@svitonline.com	155681
InterBioScreen	Jan-05	www.ibscreen.com	352641
Labotest	Apr-05	www.labotest.com	88381
Life chemicals[d]	Dec-04	www.lifechemicals.com	142653
Lithuania	01/2005[a]	www.akosgmbh.de	228369
Maybridge	Feb-05	www.maybridge.com	59497
MDPI	Feb-05	www.mdpi.net	10655
Menai	06/2004[c]	www.ryansci.com	5088
Molecular design & discovery	Nov-03	www.worldmolecules.com	33320
Moscow MedChemLabs	Feb-05	www.mosmedchemlabs.com	75581
Nanosyn	Mar-05	www.nanosyn.com	46714
Otava	Feb-05	www.otava.com.ua	80090
Peakdale	Q3/2004	www.peakdale.com	8548
Pharmeks	Mar-04	www.pharmeks.com	105602
Princeton biomolecular	Feb-05	www.princetonbio.com	488747
Pyxis discovery	Q3/2004	www.pyxis-discovery.com	3901
SALOR	Mar-04	www.sigmaaldrich.com	133532
Scientific exchange	Mar-05	www.htscompounds.com	27981
Specs	Jan-05	www.specs.net	214937
Spectrum Info	Mar-04	www.spectrum.kiev.ua	8678
TimTec	Mar-05	www.timtec.com	165521
TOSLab	Mar-05	www.toslab.com	22882
Tripos	Mar-05	www.tripos.com	82839
Vitas-M	May-05	www.vitasmlab.com	198872

[a] From ACD-SCR database (MDL).
[b] From key organics, includes Merlin and G&J collections.
[c] From Ryan scientific.
[d] Formerly I.F. Labs.
[e] After removal of duplicates, stereoisomers, entries with structural errors and saltdata.

Around 8-10 million compounds available for purchase

CHEMICAL LIBRARIES

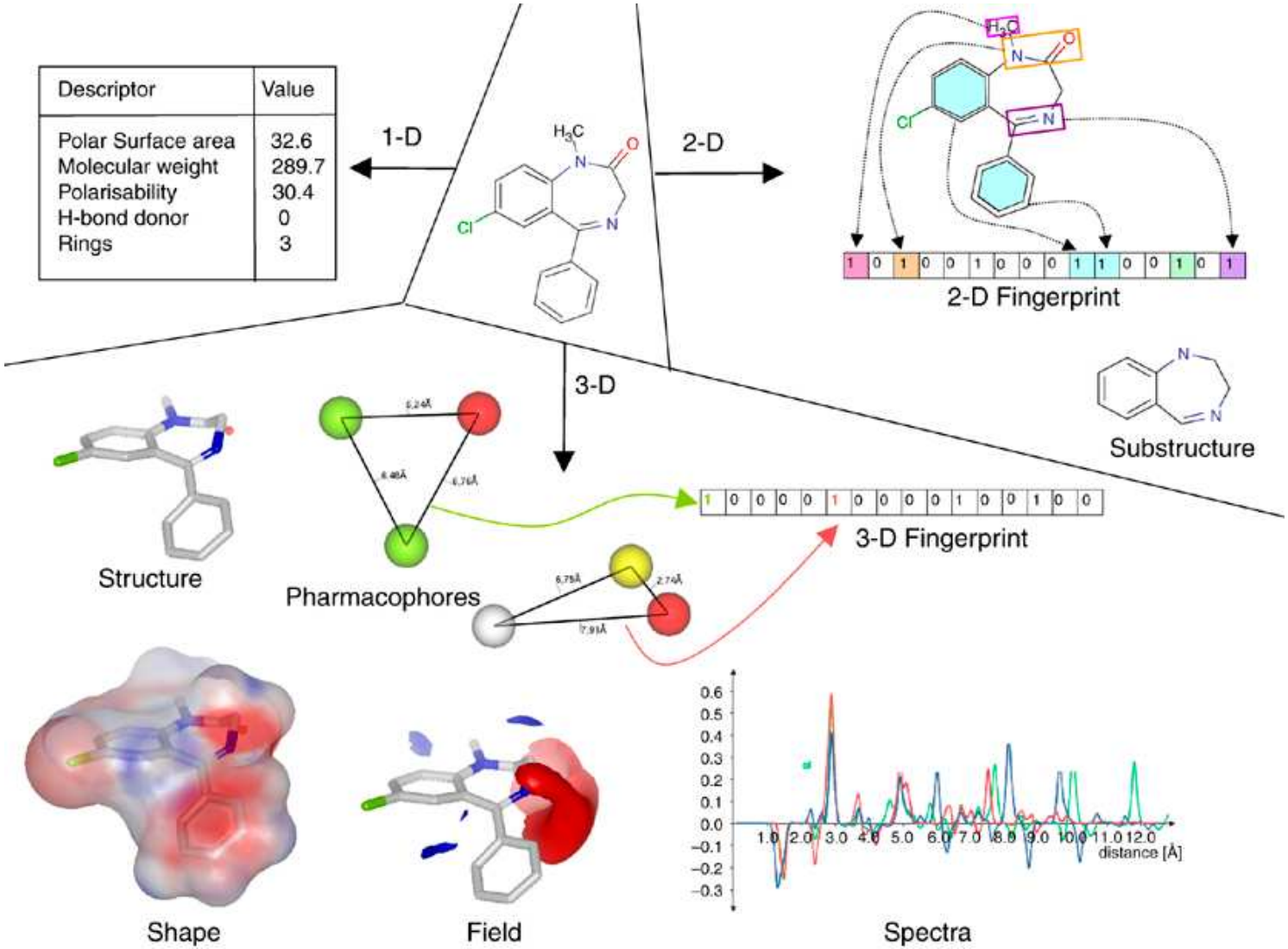
- Diversity Oriented
- Target Focused / Target Class Libraries
- Combichem Libraries
- Fragment libraries
- Drugs in market / clinical phase libraries
- ….

How to choose / select compounds from such a large pool?

British Journal of Pharmacology (2007) **152,** 38–52

Chemogenomic approaches to rational drug design

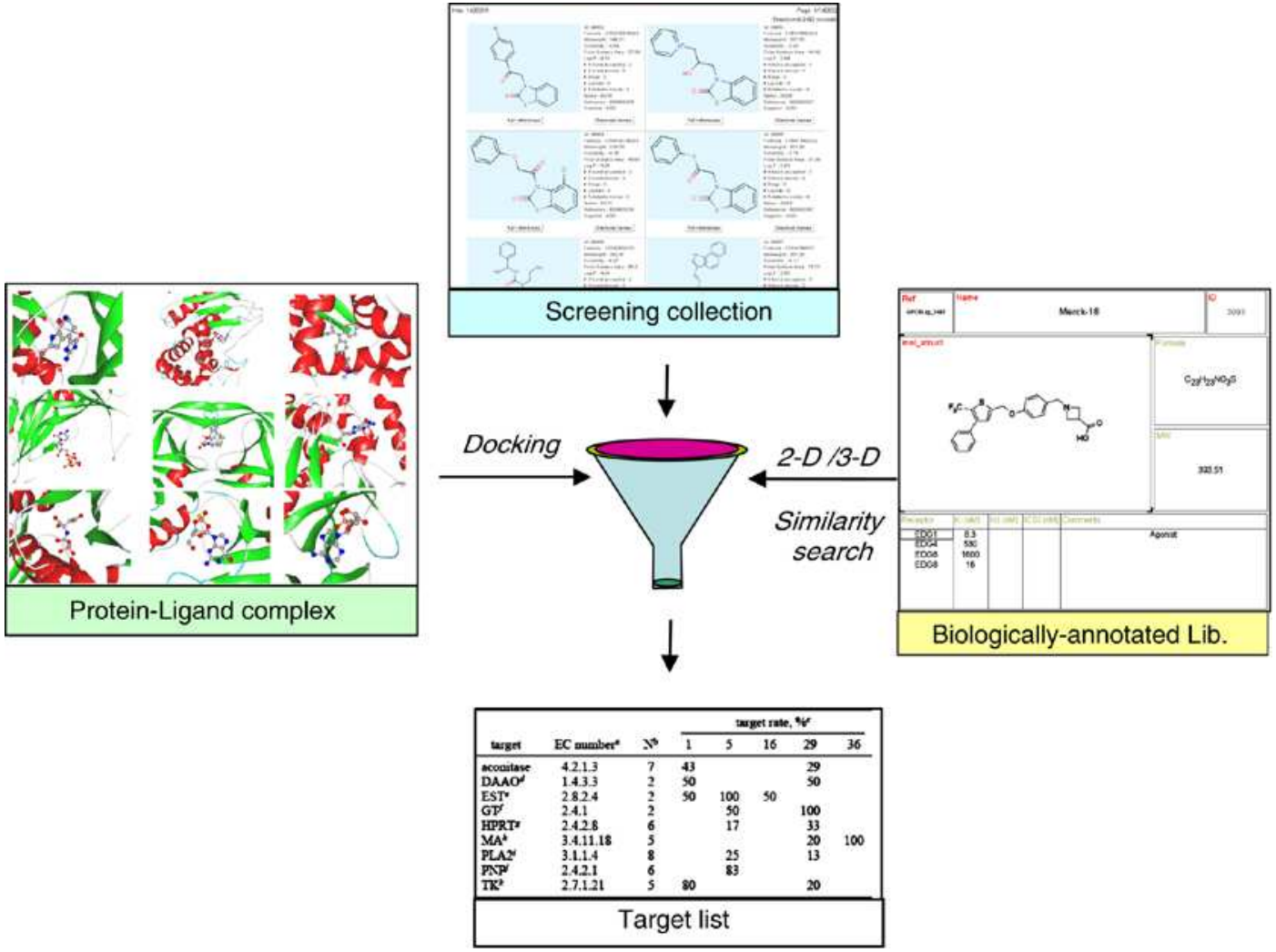
D Rognan



British Journal of Pharmacology (2007) **152,** 38–52

Chemogenomic approaches to rational drug design

D Rognan



- CHEMICAL DIVERSITY AND BIOLOGICAL DIVERSITY
- CHEMICAL LIBRARIES: AVAILABILITY / COMPOUND SELECTION
- **A CASE STUDY**

Discovery of 5-HT_6 receptor ligands based on virtual HTS

Stefan Tasler,[a,*] Jürgen Kraus,[a] Andreas Wuzik,[a] Oliver Müller,[a] Andrea Aschenbrenner,[a] Elena Cubero,[b,*] Rosalia Pascual,[b] Jordi-Ramon Quintana-Ruiz,[b] Alberto Dordal,[b] Ramon Mercè[b] and Xavier Codony[b]

[a]*4SC AG, Am Klopferspitz 19a, 82152 Planegg-Martinsried, Germany*
[b]*ESTEVE, Av. Mare de Déu de Montserrat 221, 08041 Barcelona, Spain*

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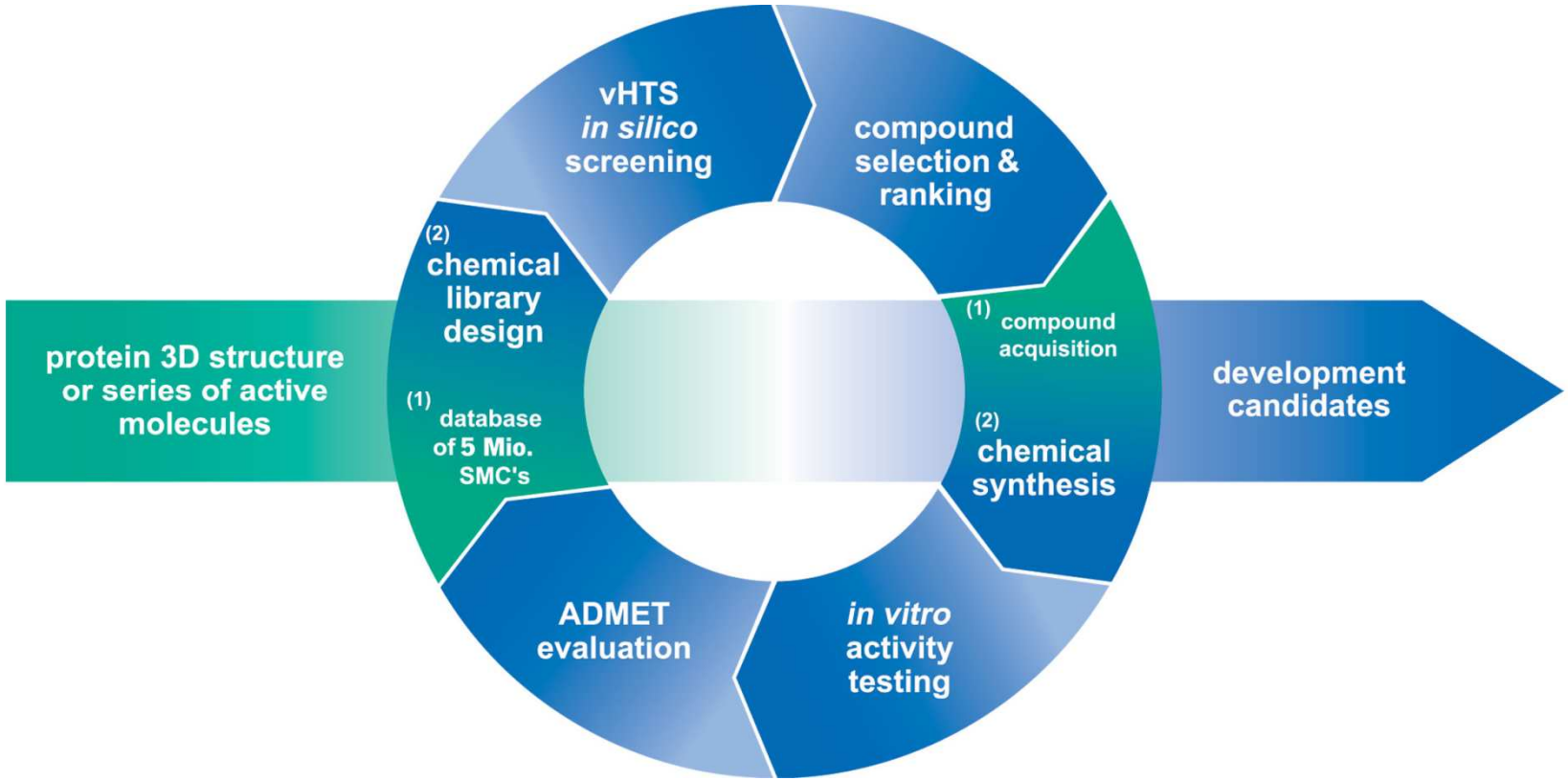
4SC, Munich, Germany (http://www.4sc.com/)



Virtual Screening Cycle

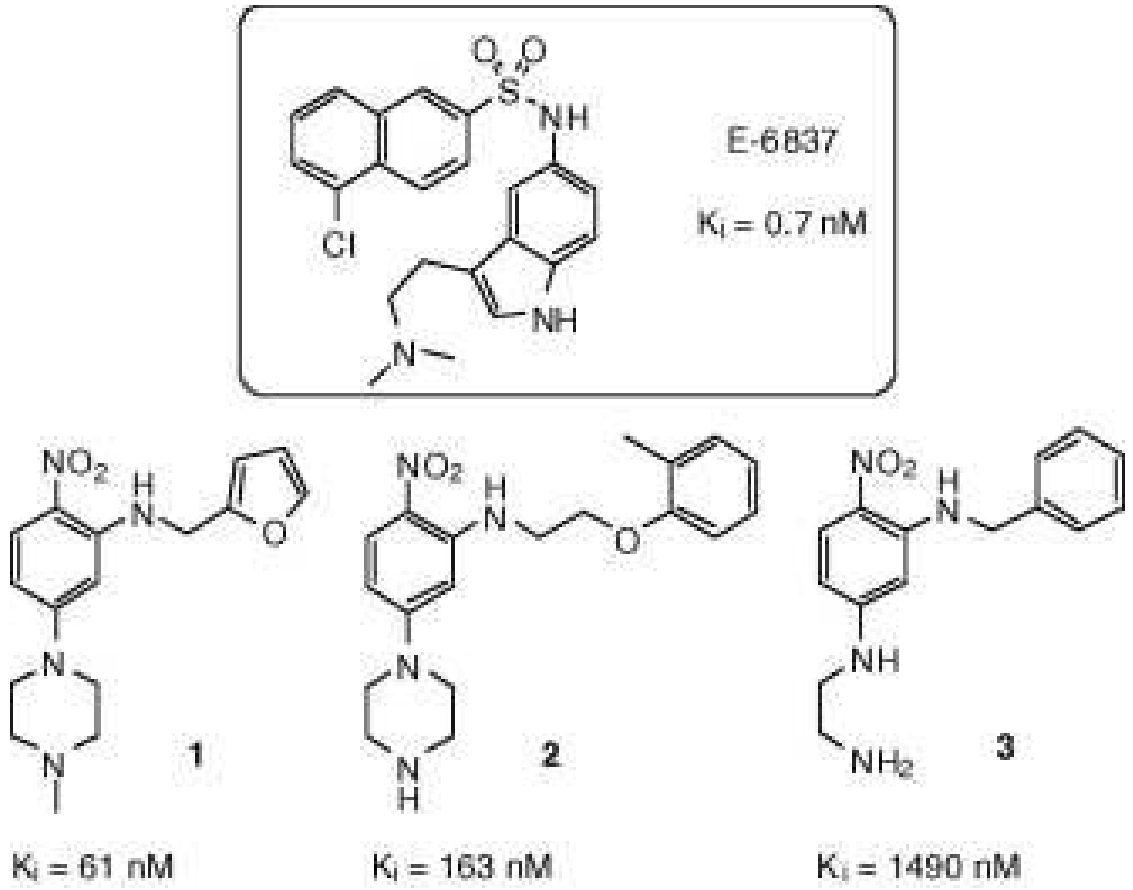
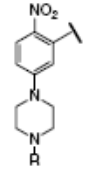
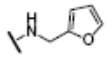
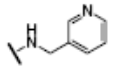
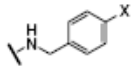
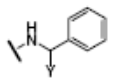
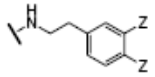


Figure 1. Template for a pharmacophore alignment and hit structures **1**–**3** from biological testing

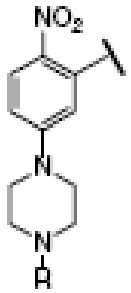
Table 1. 4-Piperazinylnitroarenes



Entry	2-Amino substituent	R = Me K_i [nM] (inhib. @ 10 μM)	R = H K_i [nM] (inhib. @ 10 μM)
1		61[a]	25[a]
2		1267	1512
			
3	X = H	— (74%)	28[b]
4	X = CI	59	8[b]
5	X = F	172[c]	n.d.
			
6	Y = Me	12[a]	— (13%)
7	Y = Ph	4489	n.d.
8		250	482
			
9	Z = H	119	33[a]
10	Z = OMe	— (24%)	— (59%)

n.d., not determined.

Table 1. 4-Piperazinylnitroarenes



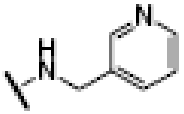
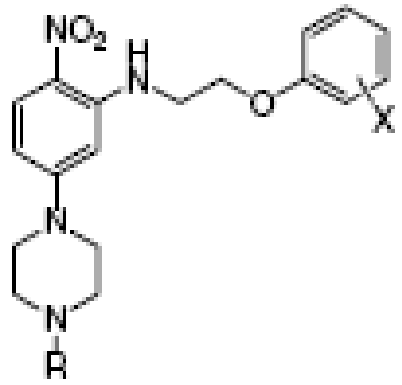
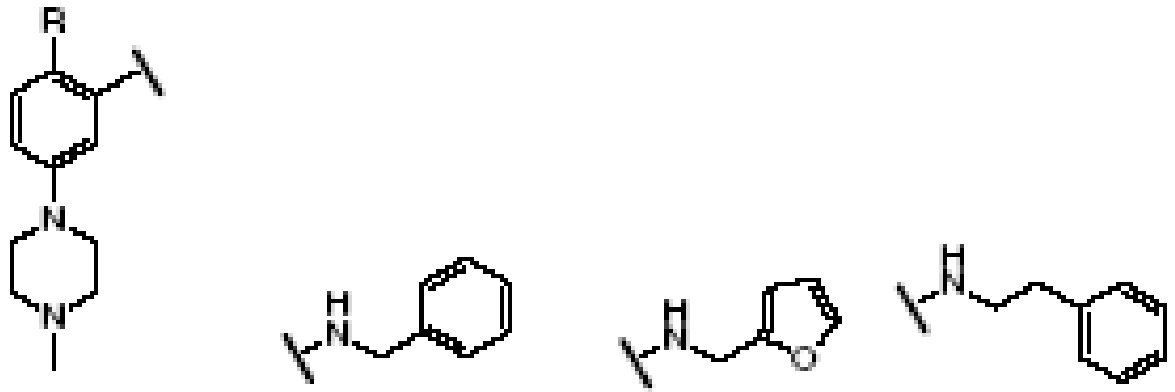
Entry	2-Amino substituent	R = Me K_i [nM] (inhib. @ 10 μM)	R = H K_i [nM] (inhib. @ 10 μM)
1		61[a]	25[a]
2		1267	1512
			
3	X = H	— (74%)	28[b]
4	X = CI	59	8[b]

Table 2. 2-(2-Aryloxyethylamino)nitroarenes



Entry	X =	R = Me K_i [nM] (inhib. @ 10 μM)	R = H K_i [nM]
11	H	n.d.	114
12	2-OMe	19[a]	
13	3-OMe	— (22%)	
14	4-OMe	245	
15	2-Me	26[a]	163
16	3-Me	— (10%)	
17	4-tBu	80	
18	3-Me, 4-Me	— (67%)	
19	4-Cl	— (21%)	290

Table 4. Substitution of the nitro head group



Entry	R =	K_i [nM] (inhib. @ 10 μM)	K_i [nM] (inhib. @ 10 μM)	K_i [nM] (inhib. @ 10 μM)
3/1/9	NO_2	— (74%)	61	119
27	CO_2Me	— (72%)	— (31%)	462
28	CO_2H	— (49%)	Inactive	Inactive
29	CN	108[a]	1365	n.d.
30	OMe	409	— (53%)	1013
31	OBn	928	402	1284

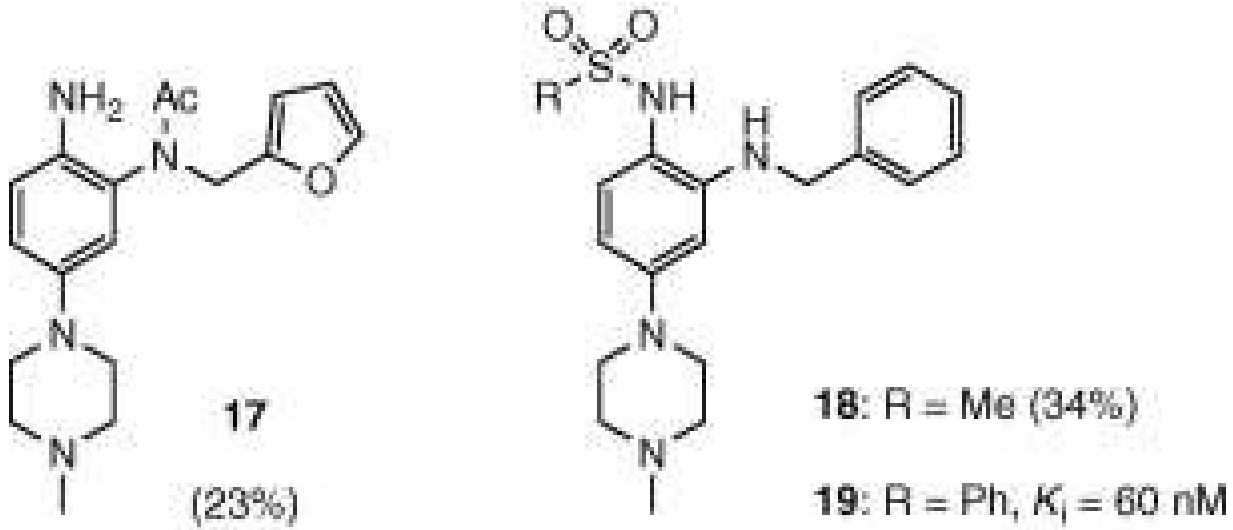
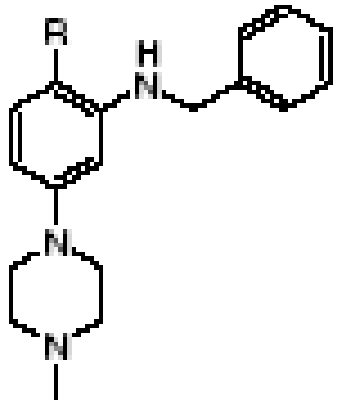


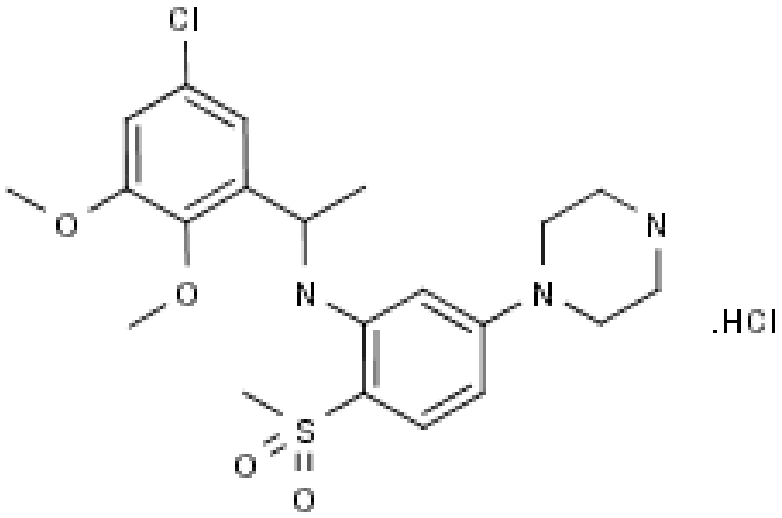
Figure 4. Aniline and sulfonamides; inhibition at 10 μM given in parentheses

Table 6. Affinity data on other receptors



Receptor	R = CN K_i [nM] (inhib. @ 1 μM)	R = $PhSO_2NH$ (19) —(inhib. @ 1 μM)
5-HT_{2A}	47	— (61%)
5-HT_{2B}	— (68%)	— (63%)
5-HT_{2C}	— (72%)	— (14%)
5-HT_7	— (52%)	— (6%)
H_1	— (65%)	— (2%)

PRX-07034 is a serotonin 5HT-6 antagonist in early clinical trials at Predix Pharmaceuticals for the treatment of cognitive impairment associated with Alzheimer's disease or schizophrenia. The compound is also under development for potential use as therapy for obesity and Alzheimer's type dementia.



PRX-07034			
2008	Phase II	Memory impairment	Epix Pharmaceuticals

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Gracias por vuestra atención!